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(21) International Application Number: PCT/GB99/02956 (22) International Filing Date: 7 September 1999 (07.09.99) (30) Priority Data: 9819472.3 7 September 1998 (07.09.98) GB (71) Applicant (for all designated States except US): CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED [GB/GB]; Cambridge House, 6-10 Cambridge Terrace, Regent's Park, London NW1 4JL (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DENNY, William, Alexander [NZ/NZ]; 165 Gossamer Drive, Pakuranga, Auckland 1706 (NZ). ATWELL, Graham, John [NZ/NZ]; 192 Gowing Drive, Meadowbank, Auckland 1005 (NZ). PALMER, Brian, Desmond [NZ/NZ]; 9 Monet Grove, West Harbour, Auckland 1008 (NZ). WILSON, William, Robert [NZ/NZ]; 102 Alfred Street, Onehunga, Auckland 1006 (NZ). (74) Agents: STUART, Ian et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 13 July 2000 (13.07.00)	
(54) Title: NOVEL NITROPHENYLAZIRIDINE COMPOUNDS AND THEIR USE AS PRODRUGS <div data-bbox="438 1155 1006 1323"><p style="text-align: right;">(A)</p></div> (57) Abstract A range of aziridin-1-yl nitrobenzamides are provided for use as prodrugs in conjunction with nitroreductase (NR) enzymes. The amides may have 1 or 2 - substituents which may be bulky and polar. For example, 5-(aziridin-1-yl) -N-[2-(4-morpholino) ethyl] -2,4-dinitrobenzamide of Formula (A) was found to be highly active against all NR+ cell lines tested.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02956

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/395 C07D203/14 C07D403/12 A61K31/415 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARTON, R. G. (1) ET AL: "Gene therapy for ovarian carcinoma using E. coli nitroreductase and CB1954." BRITISH JOURNAL OF CANCER, (1997) VOL. 76, NO. SUPPL. 1, PP. 40. MEETING INFO.: JOINT MEETING OF THE BRITISH ONCOLOGICAL ASSOCIATION, ASSOCIATION OF CANCER PHYSICIANS AND THE ROYAL COLLEGE OF RADIOLOGISTS ST. ANDREWS, SCOTLAND, UK JULY 5-8, 1997, XP000901501 abstract ----- -/-	1-7, 10, 11, 21, 23-25

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

12 April 2000

Date of mailing of the international search report

26/04/2000

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02956

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MCNEISH, I. A. ET AL: "Virus directed enzyme prodrug therapy for ovarian and pancreatic cancer using retrovirally delivered E. coli nitroreductase and CB1954" GENE THER. (1998), 5(8), 1061-1069 , XP000901446 abstract figure 6 ---	1-7,10, 11,21, 23-25
X	CONNORS T.A.: "The choice of prodrugs for gene directed enzyme prodrug therapy of cancer." GENE THERAPY, (1995) 2/10 (702-709). , XP000901500 abstract; figure 7; table 1 page 706, column 1, paragraph 2 ---	1-6,10, 11,21, 23-25
X	KHAN, ABDUL HAMEED ET AL: "Tumor-growth inhibitory nitrophenylaziridines and related compounds: structure-activity relation" CHEM.-BIOL. INTERACTIONS (1969), 1(1), 27-47 , XP000901515 abstract page 33, paragraph 2; tables 2-4 ---	1-7, 9-12, 23-25
X	KHAN, A. H. ET AL: "Tumor-growth inhibitory nitrophenylaziridines and related compounds. Structure-activity relations. II" CHEM.-BIOL. INTERACTIONS (1971), 4(1), 11-22 , XP000901517 abstract; tables 1,3 ---	1-6,14, 23-25
X	KNOX, RICHARD J. ET AL: "Bioactivation of CB 1954: reaction of the active 4-hydroxylamino derivative with thioesters to form the ultimate DNA-DNA interstrand crosslinking species" BIOCHEM. PHARMACOL. (1991), 42(9), 1691-7 , XP000901499 abstract ---	1-6,10, 11,23-25
X	LEWIS, D.F.V.: "Molecular orbital calculations on tumour-inhibitory phenyl aziridines: QSARs" XENOBIOTICA, vol. 19, no. 3, 1989, pages 341-356, XP000901493 abstract; figure 1; tables 2,9 page 343, paragraph 3 -page 352, paragraph 2 ---	1-7,10, 11,23-25
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02956

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KNOX, RICHARD J. ET AL: "A new cytotoxic, DNA interstrand crosslinking agent, 5-(aziridin-1-yl)-4-hydroxylamino-2-nitrobenzamide, is formed from 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB 1954) by a nitroreductase enzyme in Walker carcinoma cells" BIOCHEM. PHARMACOL. (1988), 37(24), 4661-9, XP000901497 abstract	1-6,10, 11,23-25
X	MCNEISH I.A. ET AL: "Gene directed enzyme prodrug therapy for cancer." ADVANCED DRUG DELIVERY REVIEWS, (1997) 26/2-3 (173-184)., XP000901495 abstract; table 1 page 177, column 2, paragraph 2; figure 4	1-6,10, 11,23-25
X	ANLEZARK G M ET AL: "BIOACTIVATION OF DINITROBENZAMIDE MUSTARDS BY AN E.COLI B NITROREDUCTASE" BIOCHEMICAL PHARMACOLOGY, GB, PERGAMON, OXFORD, vol. 50, no. 5, 1 January 1995 (1995-01-01), pages 609-618, XP000645552 ISSN: 0006-2952 abstract	1-6,10, 11,22-25
X	WO 97 24143 A (AEPACT LTD ;BURKE PHILIP J (GB); BAGSHAW KENNETH D (GB)) 10 July 1997 (1997-07-10) claim 10; example 1	1-6,10, 11,22-25
X	WO 94 21118 A (UAB RESEARCH FOUNDATION ;GARVER ROBERT I JR (US); SORSCHER ERIC J) 29 September 1994 (1994-09-29) claim 16	1-6,10, 11,22-25
X	WO 95 12678 A (CONNORS THOMAS ;KNOX RICHARD (GB); SHERWOOD ROGER (GB); CANCER RES) 11 May 1995 (1995-05-11) abstract page 8, line 30 -page 11, line 31	1-6,10, 11,22-25
X	BAILEY S M ET AL: "INVESTIGATION OF ALTERNATIVE PRODRUGS FOR USE WITH E. COLI NITROREDUCTASE IN 'SUICIDE GENE' APPROACHES TO CANCER THERAPY" GENE THERAPY, GB, MACMILLAN PRESS LTD., BASINGSTOKE, vol. 3, no. 12, December 1996 (1996-12), pages 1143-1150, XP000783673 ISSN: 0969-7128 abstract; figure 1	1-6,10, 11,22-25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02956

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 25
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-12, 21-25 relate to a large number of possible compounds/uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds/uses claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the individually claimed and the compounds 1-19 of table 1, with due regard to the general idea underlying the present application.

Regarding claim 13: According to Rule 6.2.a. PCT, claims shall not, except where absolutely necessary, rely on references to the description. Therefore, the part " compounds 2-29 set out in table 1" has been disregarded.

Regarding claims 1-12, 21-25: there is no Z in formula (I).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02950

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9724143	A	10-07-1997	EP 0869818 A	14-10-1998
			CA 2168680 A	30-06-1997
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